Case Report

Diagnosing neurodegeneration with brain iron accumulation before iron starts to accumulate

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ABSTRACT

Introduction

Neurodegeneration with brain iron accumulation (NBIA) consists of a heterogeneous group of disorders with brain iron accumulation as common radiological endpoint. Mutations in multiple genes have been associated with NBIA. We present 2 cases with a different type of NBIA, in whom the diagnosis was confirmed before brain iron accumulation became evident on MRI.

Case description

The first patient was referred because of frequent falls at the age of 4 years. She had an ataxic gait and weak Achilles tendon reflexes. Two years later, pyramidal and more prominent cerebellar signs became evident. A skin and muscle biopsy revealed intra-axonal spheroids in the peri-and endomysial myelinated nerve bundles as well as in the motor endplates, which led to the diagnosis of PLA2G6-associated neurodegeneration (PLAN). Brain iron accumulation occurred at follow-up MRI at 9 years of age.

The second patient was referred because of developmental stagnation and detection of elevated liver enzymes at 3 months of age. Seizures started at 15 months of age and were refractory to treatment with multiple anti-epileptic drugs. Molecular genetic testing using an epilepsy gene panel revealed a mutation in the *WDR45* gene, a known cause of beta-propeller protein-associated neurodegeneration (BPAN). Brain MRI at 14 months of age showed diffuse hypomyelination in the absence of BIA.

Discussion

This report highlights that NBIA can be suspected on a clinical basis and confirmed by genetic testing before iron accumulation becomes present on brain MRI. Early diagnosis will provide a longer timeframe for potential disease modulating treatments in the future.

KEYWORDS

Neurodegeneration, brain iron accumulation, PLA2G6, WDR45

Introduction

Neurodegeneration with brain iron accumulation (NBIA) is characterized by progressive motor symptoms, neurological regression and iron accumulation on brain MRI. NBIA comprises 10 subtypes including pantothenate kinase-associated neurodegeneration (PKAN), fatty acid hydroxylase-associated neurodegeneration (FAHN), mitochondrial membrane protein-associated neurodegeneration (MPAN), beta-propeller protein-associated neurodegeneration (BPAN), phospholipase A2-associated neurodegeneration (PLAN), Kufor-Rakeb syndrome, aceruloplasminemia, neuroferritinopathy, Woodhouse-Sakati syndrome and COASY protein-associated neurodegeneration. (1) The exact mechanism to explain the accumulation of iron in the brain has not yet been fully clarified. The variable clinical presentation and the accumulation of brain iron after onset of disease symptoms challenge early diagnosis in NBIA. We here present 2 unrelated cases of NBIA, which were diagnosed prior to BIA.

Case reports

Patient 1

A 4 year-old girl was referred for recurrent falls and unsteady gait since the age of 3 years. Early development was uneventful, with age appropriate acquisition of gross motor, fine motor and speech and language skills. On examination eye movements were saccadic, gait was mildly ataxic and balance was poor. She had mild proximal muscle weakness with positive Gowers' sign. Deep tendon reflexes were present although Achilles tendon reflexes were weak. Speech was normal. She had normal play but was somewhat overfamiliar in her contact with strangers. Brain MRI at 4 years of age was normal and remained so after a 3-year interval. EMG and nerve conduction studies, fundoscopy, as well as serum lactate, serum alpha-foetoprotein, serum creatine kinase and urinary catecholamines were normal. Iron and ferritin analysis were normal. Friedreich ataxia and Pompe disease were excluded. Histological examination on muscle biopsy showed a predominance of type 1 fibers compatible with a metabolic myopathy. Extensive immunohistochemical testing was normal, making a muscular dystrophy unlikely. Electron microscopy of the muscle biopsy revealed intra-axonal spheroids in the peri-and endomysial myelinated nerve bundles as well as in the motor endplates, a typical feature of PLAN (Figure 1). Mutation analysis showed the presence of bi-allelic mutations, c.1021G>A, p.(Ala341Thr) and c.2036G>T, p.(Gly679Val) in the *PLA2G6* gene of the patient. Both parents were heterozygous carriers of one of these alterations. She was started on riboflavin and physiotherapy. Brain MRI at 9 years of age showed atrophy of cerebellum and vermis and iron deposition in the globus pallidus bilaterally (Figure 2). In retrospect, claval hypertrophy was present already at 4 years of age.

Patient 2

A 6-month-old boy was referred for developmental regression, characterized by lack of eye contact and social smile since the age of 3 months. Further examination revealed elevated liver enzymes (AST, ALT and LDH), normal iron, transferrin and ferritin and normal thyroid function. Metabolic workup including serum lactate, ammonium, alfa fetoprotein, sialotransferrin isoelectric focusing, as well as urinary organic acids was normal. Cardiac function was normal. MRI of liver and spleen showed no abnormalities. Gastro-oesophageal reflux was seen on impedantiometry, but gastroscopy did not show any lesions. Brain MRI showed a delayed myelination. Because of severe hypotonia and developmental stagnation, physiotherapy was started. Development continued to progress, but more slowly compared to normal. Axial hypotonia and weak deep tendon reflexes were noticed, as well as poor reaction to visual stimulation and nystagmus. At 13 months of age, EEG showed pronounced slowing of the background activity, compatible with encephalopathy. One month later parents reported episodes of eye deviation and arm flexions. He was started on levetiracetam, followed by vigabatrin because of persisting seizures and evolution to hypsarrhythmia on EEG. Seizures were refractory to add-on treatment with topiramate and sulthiame. During follow-up, feeding difficulties and peripheral hypertonia became more prominent. Botuline toxine injections were performed because of spastic quadriplegia with bilateral coxa valga. At the age of 4 years diagnosis of central visual impairment was made. Gene panel analysis through Next Generation Sequencing (NGS) revealed a *de novo* hemizygous c.520-1G>A substitution in the *WDR45* gene, causative of BPAN. The presence of this alteration was confirmed by Sanger sequencing.

Neither of the children received blood transfusions.

Discussion

NBIA is a neurodegenerative illness consisting of ten subtypes where iron accumulation is a common factor. The key clinical findings have been summarized in Table 1. Iron is an essential element for a number of brain functions including energy production, DNA synthesis and repair, phospholipid metabolism, myelination and neurotransmitter synthesis. Damaged white brain matter is a source of abnormal iron accumulation.

PLA2G6-associated neurodegeneration (PLAN) is an autosomal recessive disorder caused by mutations in the *PLA2G6* gene, located on chromosome 22q. (2) This gene encodes the 85 kDa protein iPLA2-VI phospholipase A2 beta, which plays an important role in the maintenance of cell membrane homeostasis by phospholipid remodeling, regulation of apoptosis and catalysing glycerophospholipid hydrolysis. The normal function of VIA-iPLA2 is to protect the mitochondria against oxidative stress. Normal functioning mitochondria are essential for the high energy demand of the neuronal function. (3)

Mitochondrial dysfunction stimulates cellular iron reuptake by activation of hypoxia inducible factor 1 (HIF1). (4) Experiments in iPLA2beta knockout mice have shown that divalent metal transporter 1 (DMT1) and iron regulatory protein 2 (IRP2), molecules that are important for iron homeostasis, are both upregulated. (5)

PLAN counts for 20 % of NBIA with a prevalence of 1:1000000. It consists of 3 different phenotypes with overlapping clinical and radiological findings: classic infantile neuroaxonal dystrophy (INAD), atypical neuroaxonal dystrophy (atypical NAD) and PLA2G6-related dystonia-parkinsonism. (3) INAD is the most frequent form and has an infantile onset with death generally occurring before the age of 10. A mean disease duration of 3 years and 11 months was described in a follow-up study of 25 Chinese children. (6) Atypical NAD is rare and usually starts in early childhood, but first symptoms can develop up to 45 years of age. The third type, counting for 6.9 % of PLAN, has its onset most frequently during adolescence and patients survive into adulthood. (3)

The first patient reported here was diagnosed with atypical NAD. Presenting symptoms may vary and include gait instability, ataxia, speech delay, autistic features, followed by slow disease progression. Extrapyramidal symptoms (dystonia and dysarthria) become more prominent later in the course of the disease. Neuropsychiatric symptoms, such as impulsivity, poor attention span, hyperactivity and emotional lability, are common and were an additional clue to diagnosis in our patient. (7) Cerebellar atrophy is seen on neuroimaging at 2-3 years of age, but brain iron accumulation only becomes obvious at a later stage. (8) Treatment of seizures and neuropsychiatric symptoms are recommended. Other conservative interventions are used to optimize the quality of life. (7) Our patient was compound heterozygous for 2 mutations c.1021G>A p.(Ala341Thr) and c.2036G>T, p.(Gly679Val) in the *PLA2G6* gene. The first alteration has been reported twice in patients with INAD, who were compound heterozygous for this missense and another mutation, while the latter was reported in a single patient with PLA2G6-related dystonia-parkinsonism. (9, 10, 11)

Beta propeller associated neurodegeneration (BPAN) is an autosomal recessive disorder caused by mutations in the *WDR45* gene, localized on the Xp11.23 chromosome. This gene encodes a beta-propeller scaffold protein that plays a role in phospholipid interaction and is associated with autophagy proteins ATG2A and ATG2B. (12) In case of defective autophagy, damaged cells are not cleared, which in turn results in damage to neighboring cells. (13)

BPAN counts for 1-2 % of NBIA with a prevalence of 1-3/1000000. (14) Men and women have identical phenotypes, which can be explained by somatic mosaicism by postzygotic mutations or skewing of X-chromosome inactivation. BPAN was previously referred to as SENDA (static encephalopathy of childhood with neurodegeneration in adulthood). (12)

BPAN starts in early childhood with intellectual impairment and developmental delay, often accompanied by epileptic seizures. In the second or third decade progressive dystonia, progressive cognitive decline and parkinsonism occurs. Other common features are sleep disorders, high myopia and incontinence. (14) Elevated liver enzymes, as present in our patient, were reported only once in the literature. A possible explanation is that defects in autophagy lead to functional disorders in affected organs, including the liver. (4) In our case hypomyelination was already seen on neuroimaging at 6 months of age. In literature, iron deposition in the globus pallidus and substantia nigra, together with significant cerebral atrophy is typical for BPAN. (14) Iron accumulation can be detected on brain MRI from 6 years on. (4)

In a recent study, more than 50 patients with *WDR45* mutations were summarized. Only 8 of them are males. The hypothesis that males with a mosaic pattern of *WDR45* gene mutations and a high rate of wild type allele may present a more favorable neurological course, must be confirmed in further studies. (15) However, in a study of Takano et al. (2017) and our study, two non-mosaic hemizygous mutations are described. Remarkably, they are both affecting splicing. (16) Although both mutations are predicted to completely destroy the normal splice site, it cannot be ruled out that some level of normal protein is produced.

Brain MRI is the most sensitive method to detect BIA, but a persistent elevation of neuron specific enolase (NSE) in serum and cerebrospinal fluid was reported in a patient with BIA identified in childhood. This can be an indication of neuronal damage. To confirm the potential role of NSE as a biomarker, further analyses are necessary. (17) In the patients reported here, NSE was not analyzed.

Diagnosis of NBIA can be facilitated by careful anamnesis and clinical evaluation, brain MRI, tissue biopsy and/or genetic testing. Since brain iron accumulation usually occurs late in the course of the disease, careful clinical observation becomes even more important to guide genetic testing. In both our patients, initial brain MRI was normal, but tissue biopsy was the clue to diagnosis for the first case where the intra-axonal spheroids led to the diagnosis of PLAN. With the widespread availability of NGS techniques, early diagnosis is expected to be facilitated further in a near future, as was illustrated by the second case. (18) However, potential disadvantages of NGS include price and risk of co-incidental findings. In areas where access to NGS remains challenging, careful clinical work-up is the key to orient genetic testing.

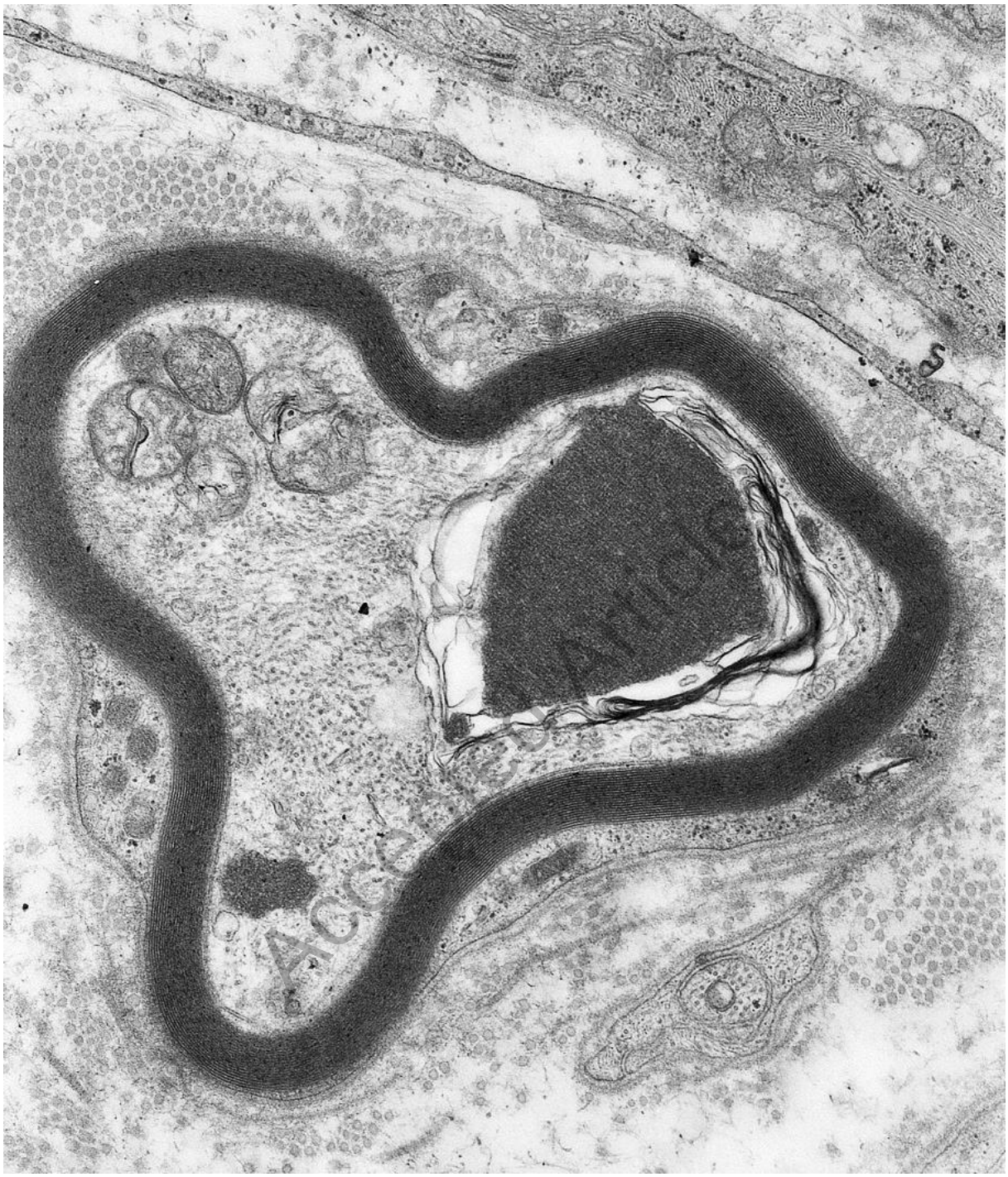
In general, treatment of NBIA consists of supportive therapies including anti-epileptic drugs for seizure control, intrathecal baclofen in case of significant dystonia, and gastric feeding tube or tracheostomy when feeding becomes impaired. (18) Recent investigations by patients with PLAN have attempted to prevent the iron accumulation in the brain by giving iron chelators. An open-label study with deferiprone resulted in a 30 % reduction of iron in the globus pallidus in a series of 9 patients, but did not result in a clinical benefit. It was not clear if the treatment duration was too short or if the neuronal damage was beyond recuperation. (19) It is hypothesized that brain iron accumulation is a secondary phenomenon and leads later to the disease of NBIA or not at all. Consequently, investigation of the clinical symptoms and genetic testing are crucial for diagnosis and to start early treatment. (20) There is one case report describing the use of L-dopa/decarboxylase inhibitor as treatment for BPAN. The rigidity and bradykinesia improved, and the patient could crawl and eat independently, but the dystonia of the lower limbs remained unchanged. (21) Further studies are needed to prove the therapeutic options of NBIA and the potential benefits of early treatment.

Conclusion

PLAN and BPAN, 2 types of NBIA, have different clinical features and can be diagnosed in different ways. It is important to suspect NBIA if clinical features of gait instability, autistic

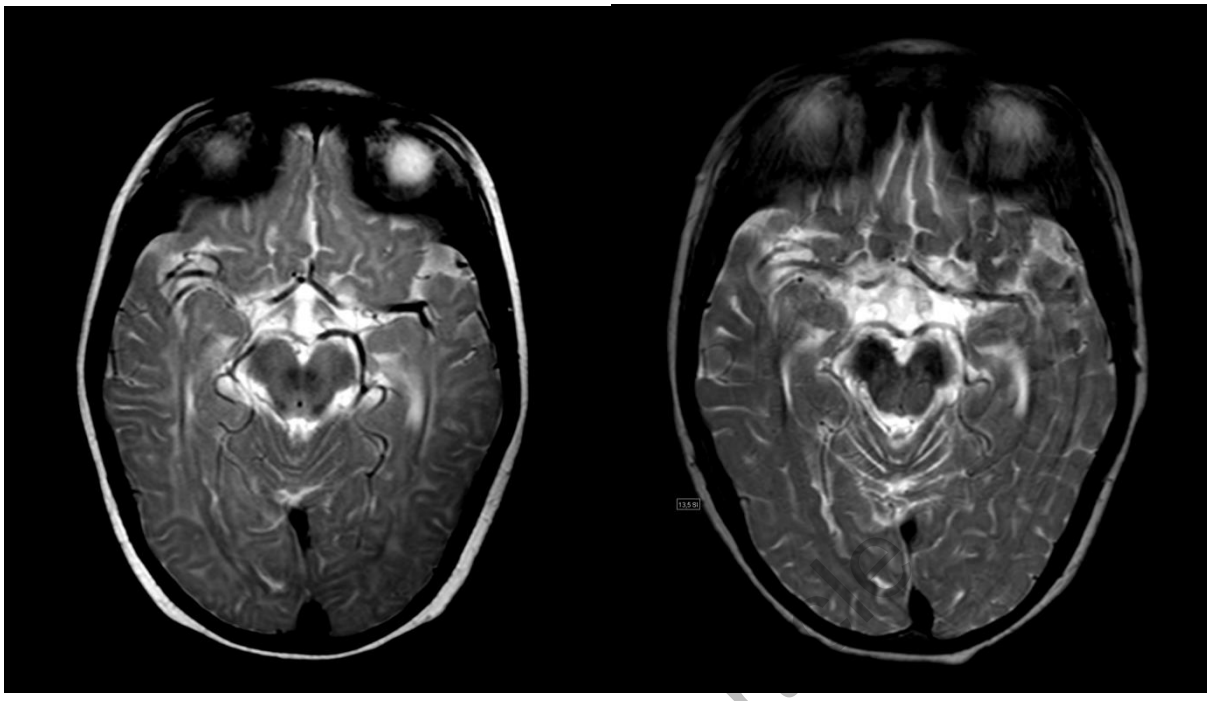
features and pyramidal symptoms for PLAN and intellectual disability and epilepsy for BPAN are present. Careful history taking, clinical examination, genetic work-up and in some cases pathology can assist with the diagnosis, before brain iron accumulation becomes visible on MRI. Further investigations are needed to improve our understanding of the pathophysiology of NBIA and develop efficient treatments. In the meantime, treatment remains conservative, aimed at comfort and prevention of secondary complications.

Figure 1



Electron microscopy: intra-axonal spheroid in a perimysial myelinated nerve bundle in Patient 1.

Figure 2



Axial T2 weighted brain MRI images of Patient 2 showing normal basal ganglia at age 1 years and hypo-intense lesions in the substantia nigra (iron deposition) at age 4 years.

Table 1

	Age of onset	*Main symptoms*	*Investigations*	*Inheritance*	*Prognosis*
PKAN	- Classic: < 6 years - Atypical: teenager-young adult	Dystonia orolingual-mandibular, spasticity	* Brain MRI: eye of the tiger sign * Electroretinography: retinal degeneration * Blood smear: acanthocytes * Genetic testing: PANK2	AR	- Classic: wheelchair before adolescence - survive until adulthood with severe disability - Atypical: normal lifespan
FAHN	Childhood	Dysarthria, gait abnormalities, dystonia, parkinsonism	* Brain MRI: iron accumulation in globus pallidus and optic atrophy * EEG: seizures can occur * Genetic testing: FA2H	AR	Loss of ambulation, visual impairment
MPAN	Childhood to early adulthood	Dysarthria, gait abnormalities, dystonia, parkinsonism	* Brain MRI: iron accumulation in globus pallidus and substantia nigra * Genetic testing: C19orf12	AR	Slow progression - survive into second decade (Rapid progression in adult-onset patients)
BPAN	Childhood	Parkinsonism, dystonia, dementia, global developmental delay	* Brain MRI: iron accumulation in globus pallidus and substantia nigra * EEG: seizures common * Genetic testing: WDR45	XLD	All patients lose ambulatory ability and become profoundly demented in adulthood
PLAN	- INAD < 3 years - Atypical NAD < 20 years	- INAD: hypotonia, visual disturbance, motor and mental retardation - atypical NAD: dystonia, dementia, parkinsonism	* Brain MRI: cerebellar atrophy and optic atrophy * Nerve biopsy: dystrophic axons * EEG: seizures occur * Genetic testing: PLA2G6	AR	- iNAD: most children die before 10 years - aNAD: slow progressive deterioration
Kufor-Rakeb	Childhood	Dystonia, parkinsonism	* Brain MRI: iron accumulation in nucleus caudatus, may occur late * Genetic testing: APT13A2	AR	Slow progression - survive until adulthood
Aceruloplasminemia	30-50 years	Diabetes, anemia, dementia, dystonia, dysarthria	* Brain MRI: iron accumulation in globus pallidus, striatum, thalamus and nucleus dentatus * Liver MRI: iron accumulation * Serum: low ceruloplasmin, copper and iron, high ferritin * Genetic testing: CP	AR	Heart failure in adulthood due to iron overload
Neuroferritinopathy	30-60 years	Dementia, dystonia, dysarthria	* Brain MRI: iron excess in basal ganglia * Serum: low ferritin	AD	Late cognitive decline
Woodhouse-Sakati	Childhood	Dystonia, deafness	* Brain MRI: iron accumulation in globus pallidus, substantia nigra	AR	Gradual progression - survive into

			* Serum: hypothyroidism, low IGF1, diabetes mellitus * Genetic testing: DCAF17		adulthood
CoPAN	Childhood	Oromandibular dystonia, dysarthria, parkinsonism, cognitive impairment	* Brain MRI: T2 pallidal hypointensity with medial hyperintensity * Genetic testing: COASY	AR	Slow progression - survive into adulthood

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Abbreviations

NBIA	Neurodegeneration with brain iron accumulation
MRI	Magnetic resonance imaging
PLAN	PLA2G6-associated neurodegeneration
BPAN	Beta-propeller protein-associated neurodegeneration
PKAN	Pantothenate kinase-associated neurodegeneration
FAHN	Fatty acid hydroxylase-associated neurodegeneration
MPAN	Mitochondrial membrane protein-associated neurodegeneration
EMG	Electromyography
EEG	Electroencephalography
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase

LDH	Lactate dehydrogenase
INAD	Classic infantile neuroaxonal dystrophy
A(typical) NAD	Atypical neuroaxonal dystrophy
SENDA	Static encephalopathy of childhood with neurodegeneration in adulthood
NSE	Neuron specific enolase
DNA	Desoxyribonucleic acid
HIF1	Hypoxia inducible factor 1
DMT1	Divalent metal transporter 1
IRP2	Iron regulatory protein 2
NGS	Next Generation Sequencing
CoPAN	COASY protein-associated neurodegeneration
AR	Autosomal recessive
AD	Autosomal dominant
XLD	X-linked dominant

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